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(21) International Application Number: PCT/US99/10251 (22) International Filing Date: 7 May 1999 (07.05.99) (30) Priority Data: 09/074,936 7 May 1998 (07.05.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/074,936 (CON) Filed on 7 May 1998 (07.05.98) (71) Applicant (for all designated States except US): SEQUENOM, INC. [US/US]; 11555 Sorrento Valley Road, San Diego, CA 92121 (US). (71)(72) Applicant and Inventor: HILLENKAMP, Franz [DE/DE]; Bahlmannstrasse 5, D-48147 Münster (DE). (72) Inventor; and (75) Inventor/Applicant (for US only): KÖSTER, Hubert [DE/US]; 8636-C Via Mallorca Drive, La Jolla, CA 92037 (US).		(74) Agent: SEIDMAN, Stephanie, L.; Heller Ehrman White & McAuliffe, Suite 700, 4250 Executive Square, La Jolla, CA 92037 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 23 March 2000 (23.03.00)
(54) Title: INFRARED MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRIC ANALYSIS OF MACROMOLECULES (57) Abstract Mixtures containing a biological macromolecule, such as a nucleic acid molecule or a polypeptide, and a liquid matrix, which absorbs infrared (IR) radiation, are provided. These mixtures are useful for analysis of the biological macromolecule by IR matrix assisted laser desorption/ionization (IR-MALDI) mass spectrometry. Also provided are processes for analyzing a biological macromolecule using IR-MALDI mass spectrometry. For example, processes for detecting the presence or identity of a biological macromolecule in a sample, or for sequencing a biological macromolecule are provided.		

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INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/US 99/10251

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C1201/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BERKENKAMP ET AL.: "PERFORMANCE OF INFRARED MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY WITH LASERS EMITTING IN THE 3 μ m WAVELENGTH RANGE" RAPID COMMUN MASS SPECTROM, vol. 11, 1997, pages 1399-1406, XP000870032	1-91, 130-134, 136, 150-152, 166,167, 169,170, 172
Y	the whole document	92-129, 135, 137-149, 153-165, 168,171, 173-226
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☒ Further documents are listed in the continuation of box C.

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INTERNATIONAL SEARCH REPORT

Int. .onal Application No

PCT/US 99/10251

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HILLENKAMP F ET AL: "MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY OF BIOPOLYMERS" ANALYTICAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. COLUMBUS, vol. 63, no. 24, page 1193-1203 XP000652496 ISSN: 0003-2700	1-91, 130-134, 136, 150-152, 166,167, 169,170, 172
Y	the whole document	92-129, 135, 137-149, 153-165, 168,171, 173-226
X	--- SIEGEL ET AL.: "CALICHEAMICIN DERIVATIVES CONJUGATED TO MONOCLONAL ANTIBODIES: DETERMINATION OF LOADING VALUES AND DISTRIBUTIONS BY INFRARED AND UV MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY AND ELECTROSPRAY IONIZATION MASS SPECTROMETRY" ANAL. CHEM., vol. 69, 1997, pages 2716-2726, XP002128444 the whole document	130-134, 136, 150-152, 166,167, 169,170, 172
X	--- BERKENKAMP ET AL.: "ICE AS A MATRIX FOR IR-MATRIX ASSISTED LASER DESORPTION/IONIZATION: MASS SPECTRA FROM A PROTEIN SINGLE CRYSTAL" PNAS, vol. 93, 1996, pages 7003-7007, XP002128445 the whole document	130-134, 136, 150-152, 166,167, 169,170, 172
Y	--- WO 96 32504 A (UNIV BOSTON) 17 October 1996 (1996-10-17) See page 44, line 14- line 18 the whole document	92-129, 135, 137-149, 153-165, 168,171, 173-226
Y	--- WO 96 37630 A (STANFORD RES INST INT) 28 November 1996 (1996-11-28) the whole document --- -/--	92-129, 135, 137-149, 153-165, 168,171, 173-226

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10251

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 33000 A (GENETRACE SYSTEMS INC) 12 September 1997 (1997-09-12) the whole document ---	92-129, 135, 137-149, 153-165, 168,171, 173-226
Y	WO 98 12355 A (GENETRACE SYSTEMS ;SHALER THOMAS A (US); TAN YUPING (US); BECKER C) 26 March 1998 (1998-03-26) the whole document ---	92-129, 135, 137-149, 153-165, 168,171, 173-226
Y	WO 96 29431 A (SEQUENOM INC) 26 September 1996 (1996-09-26) the whole document ---	92-129, 135, 137-149, 153-165, 168,171, 173-226
Y	WO 98 03684 A (HYBRIDON INC) 29 January 1998 (1998-01-29) the whole document ---	92-129, 135, 137-149, 153-165, 168,171, 173-226
Y	HAHNER ET AL.: "MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY (MALDI) OF ENDONUCLEASE DIGESTS OF RNA" NUCLEIC ACIDS RESEARCH, vol. 25, no. 10, 1997, pages 1957-1964, XP002128446 the whole document ---	92-129, 135, 137-149, 153-165, 168,171, 173-226
A	WO 95 15001 A (WATERS CORP ;DORSCHER CRAIG A (US); JARRELL JOSEPH A (US); TOMANY) 1 June 1995 (1995-06-01) the whole document ---	
A	OVERBERG A ET AL: "MATRIXUNTERSTUETZTE LASERDESORPTIONS-MASSENSPEKTROMETRIE: EINE EMPFINDLICHE ANALYSETECHNIK FUER MAKROMOLEKUELE" LASER UND OPTOELEKTRONIK,DE,FACHVERLAG GMBH. STUTTGART, vol. 24, no. 1, 1992, pages 50-58, XP000247328 ISSN: 0722-9003 the whole document ---	
	-/--	

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/US 99/10251

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>NORDHOFF ET AL.: "MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY OF NUCLEIC ACIDS WITH WAVELENGTHS IN THE ULTRAVIOLET AND INFRARED" RAPID COMMUN MASS SPECTROM, vol. 6, 1992, pages 771-776, XP000870028 the whole document</p> <p>---</p>	
A	<p>NELSON R W ET AL: "TIME-OF-FLIGHT MASS SPECTROMETRY OF NUCLEIC ACIDS BY LASER ABLATION AND IONIZATION FROM A FROZEN AQUEOUS MATRIX" RAPID COMMUNICATIONS IN MASS SPECTROMETRY,GB,LONDON, vol. 4, no. 9, 1990, page 348-351 XP002072976 the whole document</p> <p>---</p>	
A	<p>NORDHOFF E ET AL: "DIRECT MASS SPECTROMETRIC SEQUENCING OF LOW-PICOMOLE AMOUNTS OF OLIGODEOXYNUCLEOTIDES WITH UP TO 21 BASES BY MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY" JOURNAL OF MASS SPECTROMETRY,GB,WILEY, CHICHESTER, vol. 30, no. 1, 1995, page 99-112 XP002047878 ISSN: 1076-5174 the whole document</p> <p>---</p>	
A	<p>NORDHOFF ET AL.: "COMPARISON OF IR-AND UV-MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY OF OLIGODEOXYNUCLEOTIDES" NUCLEIC ACIDS RESEARCH, vol. 22, no. 13, 1994, pages 2460-2465, XP002128447 the whole document</p> <p>---</p>	
A	<p>NORDHOFF E: "Matrix-assisted laser desorption/ionization mass spectrometry as a new method for the characterization of nucleic acids" TRAC, TRENDS IN ANALYTICAL CHEMISTRY,GB,ANALYTICAL CHEMISTRY. CAMBRIDGE, vol. 15, no. 6, 1996, page 240-250 XP004034771 ISSN: 0165-9936 the whole document</p> <p>---</p>	

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10251

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TANG K ET AL: "MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY OF IMMOBILIZED DUPLEX DNA PROBES" NUCLEIC ACIDS RESEARCH,GB,OXFORD UNIVERSITY PRESS, SURREY, vol. 23, no. 16, 1995, page 3126-3131 XP002016562 ISSN: 0305-1048 the whole document	
P,Y	WO 98 20166 A (DEN BOOM DIRK VAN ;JURINKE CHRISTIAN (DE); HIGGINS G SCOTT (DE); L) 14 May 1998 (1998-05-14) the whole document	92-129, 135, 137-149, 153-165, 168,171, 173-226
P,X	BERKENKAMP ET AL.: "INFRARED MALDI MASS SPECTROMETRY OF LARGE NUCLEIC ACIDS" SCIENCE, vol. 281, July 1998 (1998-07), pages 260-262, XP002128448 the whole document	1-91, 130-134, 136, 150-152, 166,167, 169,170, 172
P,X	BERKENKAMP ET AL.: "INFRARED MALDI-MS OF LARGE NUCLEIC ACIDS" 46TH ASMS CONFERENCE ON MASS SPECTROMETRY AND ALLIED TOPICS, 21 May 1998 (1998-05-21), XP002128449 ORLANDO,USA the whole document	1-91, 130-134, 136, 150-152, 166,167, 169,170, 172
P,X	KIRPEKAR ET AL.: "DOUBLE STRANDED DNA ANALYSED BY UV- AND IR-MALDI-MS" 46TH ASMS CONFERENCE ON MASS SPECTROMETRY AND ALLIED TOPICS, 21 May 1998 (1998-05-21), XP002128450 the whole document	1-91, 130-134, 136, 150-152, 166,167, 169,170, 172

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/10251

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9632504 A	17-10-1996	AU 5544696 A CA 2218188 A EP 0830460 A JP 11503611 T	30-10-1996 17-10-1996 25-03-1998 30-03-1999
WO 9637630 A	28-11-1996	US 5700642 A US 5830655 A AU 695705 B AU 5635296 A CA 2220418 A CN 1191575 A DE 69605669 D EP 0828855 A JP 11505127 T	23-12-1997 03-11-1998 20-08-1998 11-12-1996 28-11-1996 26-08-1998 20-01-2000 18-03-1998 18-05-1998
WO 9733000 A	12-09-1997	AU 2069597 A CA 2248084 A EP 0886681 A	22-09-1997 12-09-1997 30-12-1998
WO 9812355 A	26-03-1998	US 5965363 A AU 4591697 A	12-10-1999 14-04-1999
WO 9629431 A	26-09-1996	US 5605798 A AU 5365196 A CA 2214359 A CN 1202204 A EP 0815261 A JP 11508122 T	25-02-1997 08-10-1996 26-09-1996 16-12-1998 07-01-1998 21-07-1999
WO 9803684 A	29-01-1998	AU 4042597 A	10-02-1998
WO 9515001 A	01-06-1995	CA 2205040 A EP 0764264 A	01-06-1995 26-03-1997
WO 9820166 A	14-05-1998	US 5900481 A AU 5106998 A EP 0954612 A NO 992168 A AU 5247298 A DE 19782097 T EP 0937097 A NO 992167 A WO 9820019 A AU 5198098 A EP 0937096 A NO 992169 A WO 9820020 A	04-05-1999 29-05-1998 10-11-1999 06-07-1999 29-05-1998 14-10-1999 25-08-1999 05-07-1999 14-05-1998 29-05-1998 25-08-1999 06-07-1999 14-05-1998

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